Remarks

Claims 1-23 are pending. Claims 8-19 have been withdrawn from consideration by the Examiner. Claims 1-7 and 20-23 are currently under consideration. Reconsideration of rejections applied to these claims is respectfully requested.

Claim Rejections 35 U.S.C. §101 and §112, 1st paragraph

The office action states that the rejection of Claims 1-7 under 35 U.S.C. §101 and §112, 1st paragraph, is maintained and applied to claims 20-23.

Applicant respectfully traverses on the grounds that Applicant contends a credible, specific and substantial utility for the claimed antibody has been disclosed in the instant application, as required under 35 U.S.C. §101 and §112, 1st paragraph. The instant invention is drawn to an antibody that binds to a protein receptor comprising SEQ ID NO:2 and a composition comprising the antibody, the protein receptor comprising SEQ ID NO:2 being claimed by Applicant in patent 6,790,626, from which patent the instant application claims priority.

The office action states that the art recognized utility for UTP does not render the instant claimed invention a specific and substantial utility because "there is no structural or functional link between UTP and antibody that binds to the protein comprising SEQ ID NO:2". However, the office action acknowledges the art recognized utility that UTP is known in the art as a therapeutic for cystic fibrosis. The specification exemplifies that P2Y4 receptors mediate the actions of intracellular UTP, and discloses that P2Y4 receptors are a therapeutic target for the treatment of cystic fibrosis.

Applicant respectfully submits that the P2Y4 receptor (SEQ ID NO:2) identified by Applicant is the structural and functional link that binds UTP and that binds an antibody, an antagonist antibody, e.g., an antibody that would interrupt the binding of UTP to the P2Y4 receptor, and an agonist antibody, e.g., an antibody that would mimic the binding of UTP's binding to the P2Y4 receptor. One is reminded of the relatively low bar set for utility as outlined in the following excerpt from Section 2107.03 of the MPEP:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the

> activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, ***all that is required is a reasonable correlation between the activity and the asserted use***. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980). (emphasis added)

The office action states that as of the invention date, Moore et al. teaches that UTP activates P2Y4 as well as other receptors, e.g., P2Y2, on the one hand, yet also states that "there is no evidence on the record showing that UTP is the natural ligand of the receptor of SEQ ID NO:2". To clarify, (Robaye et al. 2003) identified a luminal P2Y4 receptor as responsible for UTP-activated Cl− secretion in the small intestine. Further, Applicant notes that the specification discloses that the polypeptide of SEQ ID NO:2 is a UTP receptor, and that incubation of cells expressing the polypeptide of SEQ ID NO:2 with UTP causes the accumulation of inositol tri-phosphate, as illustrated in Figure 4 of the instant application.

The office action also states that there is no evidence on the record that UTP exerts such a therapeutic effect via the protein receptor comprising SEQ ID NO:2. However, the therapeutic effect of a drug composition does not have to be proven to meet the utility requirement, see above quote from the MPEP, only a correlation is required. Applicant maintains that there is a reasonable correlation between the activity in question (UTP mediated signaling of $P2Y_4$ (SEQ ID NO:2)), and the asserted utility (therapeutic for cystic fibrosis), and thus the claimed antibody has a credible, specific and substantial use.

The office action states that the Applicant's arguments are not deemed persuasive, for three general reasons

1) ***Effective filing date***

The office action asserts on page 3 of the office action that the effective filing date of the instant application is considered to be 11/12 1998, i.e. the filing date of 09/077,173. Applicant respectfully notes that 09/077,173 is a 371 National Stage Entry of PCT/BE96/00123 and thus has an effective filing date of 11-21-1996, and claims the benefit of foreign priority to November 21, 1995. Therefore, the effective filing date of the instant application is November 21, 1996.

In referring to the top of page 9 of Applicant's most recently filed response, the office action that all cited references are after the effective filing date of the instant application (page 4, lines 4-7 of the instant office action). Applicant respectfully disagrees, noting that the two references cited by Applicant were a 1991 article by Knowles and a 1994 article by Clarke et al. see excerpt below. These references are not prior art as suggested by the office action. However, these references reflect the state of the art at the time of Applicant's invention:

> "Robaye et al. teaches prior to the effective filing date of the instant application, it was known that one important action of extracellular ATP and UTP is to stimulate the transepithelial secretion of chloride as a result of increased apical permeability, **referencing a 1991 article by Knowles**, see first paragraph of discussion. Robaye et al. also teaches that this process is mediated by an inositol triphosphate mediated increase in cystolic Ca+2 that induces the opening of outwardly rectifying chloride channels, **referencing a 1994 article by Clarke et al.**, see first paragraph of Robaye et al.'s discussion, consistent with the instantly disclosed accumulation of inositol tri-phosphate upon incubation of cells expressing the polypeptide of SEQ ID NO:2 with UTP (Figure 4 of the instant specification).
>
> The combined teachings of these references provide a reasonable correlation between the activity in question (UTP signaling mediated through cell surface $P2Y_4$ (SEQ ID NO:2)), and the asserted utility (treating cystic fibrosis). That is, the actions of extracellular nucleotides (UTP) are mediated by $P2Y_4$ receptors as disclosed in the specification, and that $P2Y_4$ receptors are a pharmocotherapeutic target for the treatment for cystic fibrosis, as asserted in the specification. Therefore, Applicant submits there is disclosed a real world link between the claimed antibodies to $P2Y_4$ (SEQ ID NO:2), and the asserted utility of their being used as a pharmaceutical composition in the treatment of cystic fibrosis."

2) ***Real world context of use***

The second reason the office action finds Applicant's arguments not persuasive is that the "asserted utilities are not specific and substantial because they do not identify or reasonably confirm a real world context of use". One is reminded of the MPEP's

guidance above that states in part that: "the applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty". The referenced asserted utility is the assertion that the polypeptide of SEQ ID NO:2 is a pyrimidinergic receptor, preferably a UTP receptor, and an agonist or antagonist may be used in a pharmaceutical composition in the treatment of cystic fibrosis. Applicant contends that treating cystic fibrosis is a specific and real world use.

The office action states that an assertion that an agonist or antagonist may be used in a pharmaceutical composition in the treatment of cystic fibrosis is a clear invitation for further research because either an agonist or antagonist, but not both, may be used for treatment of cystic fibrosis. Applicants respectfully disagree. Applicant notes there may be situations where either an antagonist or an agonist antibody or both an antagonist and an agonist antibody may be used in treatment of cystic fibrosis. Cystic Fibrosis patients have a mutation in the CFTR gene that leads to a defect in cAMP stimulated chloride transport, see pages 8-9 of most recently filed response. As noted in both pre and post filing date references, defects in CFTR destroy or reduce the ability of epithelial cells in the airways, sweat glands, pancreas and other tissues to secret Cl in response to cAMP-mediated agonists and impair activation of apical membrane channels by cAMP-dependent protein kinase A (PKA). See Frizell et al., Trends Neurosci 10:190 (1987); Welsh, FASEB J. 4:2718 (1990). By taking advantage of P2Y4's capacity to act as a cAMP dependent chloride secretogue, an antibody that mimics UTP, e.g., an agonist antibody, may be effective in treating Cystic Fibrosis. Further, an antagonist antibody may be used in titrating an over-abundance of an administered P2Y4 agonist, in vivo.

Applicant respectfully disagrees with the office action's further statement that the specification does not identify the biological functions of the polypeptide of SEQ ID NO: 2. The specification discloses that the polypeptide of SEQ ID NO:2 is a UTP receptor, that incubation of cells expressing the polypeptide of SEQ ID NO:2 with UTP causes the accumulation of inositol tri-phosphate in Figure 4, and that an agonist or antagonist may be used in a pharmaceutical composition in the treatment of cystic fibrosis. Applicant submits that a low bar is set for utility and that a correlation, not necessarily a "causative link" between the polypeptide of SEQ ID NO:2 and cystic fibrosis is required. Applicant notes that in most cases, an Applicant's assertion of utility creates a

presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101. See, e.g., *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

The MPEP § 2107.02, under the heading "The Claimed Invention Is The Focus Of The Utility Requirement," states

- "Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965)," and
- "Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true".

3) ***well established utility***

The office action presents a third reason for maintaining the rejection that being that the sequence and prior art search doe not reveal that the polypeptide of SEQ ID NO:2Applicant respectively notes that a well established utility is required only if there is no asserted utility disclosed in the specification, unlike the instant situation. Applicant is not asserting that there was a well established utility at the time of the invention. Applicant is asserting that the use of claimed invention as a therapeutic in cystic fibrosis,

Despite the ongoing research on the functional activities of the P2Y4 receptor, no post filing reference cited is inconsistent with Applicant's assertion of its utility as a therapeutic in cystic fibrosis. Therefore, Applicant respectfully contends that the office action's conclusion that the functional activities of the P2Y4 receptor is unclear and the claimed invention's not useful in its current form under 35 U.S.C. 101 is not an appropriate conclusion.

Conclusion

The combined teachings of these references provide a reasonable correlation between the activity in question (UTP signaling mediated through cell surface $P2Y_4$ (SEQ ID NO:2)), and the asserted utility (treating cystic fibrosis). That is, the actions of extracellular nucleotides (UTP) are mediated by $P2Y_4$ receptors as disclosed in the specification, and that $P2Y_4$ receptors are a pharmocotherapeutic target for the treatment

for cystic fibrosis, as asserted in the specification. Therefore, Applicant have disclosed a real world link between the claimed antibodies to $P2Y_4$ (SEQ ID NO:2), and the asserted utility of their being used as a pharmaceutical composition in the treatment of cystic fibrosis. In light of these remarks, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims rejection under 35 USC 112, 1st paragraph (written description)

The rejection of claims 2 and 3 under 35 USC 112, 1st paragraph (written description) is maintained and applied to new claims 20-23.

The office action states that the instant disclosure fails to provide an adequate description for an antibody that is an agonist or antagonist of the polypeptide comprising SEQ ID NO:2, and contends that the specification does not disclose the structural features of an antibody that acts as an agonist or antagonist. The office action further notes that the specification does not disclose a single antibody that is antagonist or antagonist of the polypeptide comprising SEQ ID NO:2.

Applicant respectfully traverses. In *Falkner vs. Inglis* 448 F.3d. 1357.07 (Fed Circuit 2006) the court had to consider whether claims directed to a vaccine comprising a mutant pox virus were adequately described by Inglis' specification. The court stated that examples were not necessary to support the adequacy of written description, that the written description requirement maybe met even where actual reduction to practice of an invention is absent and that there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. At the time of filing of the instant invention, making antibodies and screening them for antagonist or agonist properties in functional assays was a well developed technology. The specification exemplifies *in vitro* assays that produce a clear readout--accumulation of inositol tri-phosphate upon incubation of cells expressing the polypeptide of SEQ ID NO:2 with UTP (Figure 4 of the instant specification). This assay can be used to screen for agonist and antagonist antibodies. Thus, the highly evolved antibody technology, in combination with the disclosed functional assay and asserted utility for antagonists and agonists, puts applicant in possession of the claimed agonist and antagonist antibodies.

The office concludes from the disclosure in the specification that no specific antagonist was available for any P2Y subtype at the time of filing of the instant application, that producing an antibody that acts as an agonist or an antagonist of the invention is not conventional in the art. Applicant notes that this disclosure is background information relating to the state of the art before Applicant's invention, i.e. before 1996, and serves to promote the importance of Applicant's invention.

Again, the structure of antibodies, including agonist and antagonist antibodies, was well established at the time of the invention. One of skill in the art would be able to select for agonist and antagonist antibodies of $P2Y_4$ by measuring the level of inositol tri-phosphate the incubation of cells expressing the polypeptide of SEQ ID NO:2 with UTP, see Figure 4 of the specification. Because the specification "describes the invention with sufficient relevant identifying characteristics that such a person skilled in the art would recognize that the inventor had possession of the claimed invention" (*Pfaff v. Wells Electronics*, Inc. 525 U.S. 55), Applicants respectfully submit that Applicants were in possession of the claimed antibody molecules, and respectfully request reconsideration of the rejection.

Conclusion

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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